REMARKS UNDER 37 CFR § 1.111

Claims 2-5, 7-14, 17-24 and 26 were previously pending in the application and under examination. Claim 17 has now been cancelled, other claims have been amended, and claims 27-31 have been added. The amendments and new claims are supported in the claims as previously presented, and on page 19, line 22 ff. of the specification. Accordingly, no new matter is introduced. Claims 2-5, 7-14, and 18-31 are under examination.

Applicants are grateful to the Examiner for entering the previous amendment, converting from product claims to method claims.

Reconsideration and allowance of the application is respectfully requested.

Rejections under 35 USC §112, ¶ 2

Claims 19 and 20 stand rejected for use of the term "unrelated". However, anyone skilled in the art will know that whether tissues or cells are from related human "donors" can be routinely determined by forensic DNA analysis. Inheritance of the HLA complex between related family members results virtually always in inheritance of the entire complex *together from the same chromosome,* including the same allotypes for all the HLA-A, -B, -C, -DP, -DQ, and –DR locuses. The meaning of the term would be clear and easily tasted by the skilled reader, and therefore meets the clarity requirements of § 112 ¶ 2.

Claims 21 and 22 have now been amended to remove the term objected to.

Withdrawal of both these rejections is respectfully requested.

Double patenting

The double patenting rejections are acknowledged. Applicants will file terminal disclaimers or undertake other appropriate action upon indication that the application is otherwise in condition for allowance.

Rejection under 35 USC § 102

Applicants gratefully acknowledge withdrawal of the § 102 rejection with respect to the publication by Philips et al. (J. Exp. Med. 159:993, 1984).

Independent claims 19-20 and certain claims depending therefrom stand rejected as anticipated by Kohler et al. (Cancer Immunol. Immunother. 26, 74, 1988).

Applicants respectfully disagree. Based on the experiments performed, the donor lymphocytes in Kohler's proposed therapy would be *haploidentidal* to the subject being treated. Claims 19 and 20 both require that the donor be *unrelated* to the patient being treated. No reasonable interpretation of the term "unrelated" includes the situation where the donor and the treated subject are haploidentical. Claim 8 further requires that *both* HLA-DR antigens be different.

Withdrawal of this rejection is requested.

Rejection under 35 USC § 103(a)

Independent claims 19-22 and certain claims depending therefrom stand newly rejected as obvious over Kruse et al. (Proc. Natl. Acad. Sci. USA 87:9577, 1990).

Applicants respectfully disagree. Without making any admission as to the patentability of the claims as previously presented, claims 19 and 20 are amended herein to require that the composition contain alloactivated lymphocytes from two or more donors unrelated to the patient being treated. This is not taught or suggested in the Kruse article. In the cell populations tested by Kruse, stimulator lymphocytes were inactivated, and there were never any more than one responder population to become alloactivated.

Without making any admission as to the patentability of the claims as previously presented, claims 21 and 22 are amended herein to require that the lymphocytes in the population be allogeneic to the subject being treated. This is also not taught or suggested in the Kruse article. The tumor-specific cytotoxic T lymphocytes tested in the article were *syngeneic* to the subject being treated, not *allogeneic*. It is doubtful whether there would be any tumor antigen left in association with Kruse's anti-9L CTLs after these CTLs had lysed the 9L tumor cells used in the culture as stimulators.

The exact sequence of administration of the 9L tumor cell challenge, and the CTL therapy, is not entirely clear in the article. Even supposing the 9L cells and CTLs were mixed together in the first injection, as the Office Action apparently supposes, the tumor cells were *live*, and their purpose was to *create* cancer in the test animals, not to treat cancer. In this

circumstance, the animals *would not have had cancer* before the injection. In subsequent doses, the CTLs were injected alone. The skilled reader would understand that any application of this animal model to therapy in humans would be to treat patients *already having cancer.* Claims 20 and 22 have been amended to indicate this explicitly. Application of the Kruse therapy to human patients would involve administering the therapeutic CTLs *on their own*, not mixed with live tumor cells to create a tumor which the patient already has.

In contrast, tumor associated antigen (TAA) is included in some of the pharmaceutical compositions in the invention claimed in this application for an entirely different reason. As explained in the specification, the administered lymphocytes are believed to recruit the host immune system, which then reacts against the TAA in the composition as bystander antigen — thereby eliciting an anti-tumor immunological response. The TAA is present as inactivated tumor cells, cell extract, or isolated antigen (not live tumor cells), so as not to pose an additional risk to the patient.

The other rejected claims depend from claims 19-22, and are patentable for the same reasons. Other features that distinguish from the Kruse article include the use of inactivated tumor cells (claims 7, 30, and 31); formulation of the composition so as to elicit an immune response (claims 9, 20, 22, and 26); administration by endoscopy (claim 18); administration to a site distal to the tumor (claim 24 and 26); formulation for subcutaneous or intramuscular administration (claim 26); and use of allogeneic tumor cells (claim 31).

Withdrawal of this rejection is respectfully requested.

The application is believed to be in condition for allowance. However, should the Examiner determine that there are any remaining issues to address, applicants hereby request an interview.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-005CIP.

Respectfully submitted,
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